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10/528,833	06/16/2006	David Durantel	P08599US00/BAS	3759

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,833	DURANTEL ET AL.	
	Examiner	Art Unit	
	SAMUEL WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *31-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☒ Claim(s) *9,10,14,16 and 17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 March 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/16/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-30, and the primers of SEQ ID NOS: 1, 13, 15 and 17, in the reply filed on 06/03/2008 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 31-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 06/03/2008.

Priority

In the declaration submitted on 06/16/2006, Applicant has answered "YES" in the box indicating "Priority Not Claimed". This box is to be checked for "any foreign application for patent, inventor's certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed" (see declaration).

Receipt is acknowledged of a certified copy of the 02356188.9 application referred to in the declaration. If this copy is being filed to obtain the benefits of the foreign filing date under 35 U.S.C. 119(a)-(d), applicant should also file a claim for such priority as required by 35 U.S.C. 119(b). If the application being examined is an original application filed under 35 U.S.C. 111(a) (other than a design application) on or after

November 29, 2000, the claim for priority must be presented during the pendency of the application, and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior foreign application. See 37 CFR 1.55(a)(1)(i). If the application being examined has entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the claim for priority must be made during the pendency of the application and within the time limit set forth in the PCT and Regulations of the PCT. See 37 CFR 1.55(a)(1)(ii). Any claim for priority under 35 U.S.C. 119(a)-(d) or (f) or 365(a) or (b) not presented within the time period set forth in 37 CFR 1.55(a)(1) is considered to have been waived. If a claim for foreign priority is presented after the time period set forth in 37 CFR 1.55(a)(1), the claim may be accepted if the claim properly identifies the prior foreign application and is accompanied by a grantable petition to accept an unintentionally delayed claim for priority. See 37 CFR 1.55(c).

Claim Objections

Claims 9, 10, 14 and 16 are objected to because they recite SEQ ID NOS that were not elected. These claims will only be examined with regard to the elected sequences of SEQ ID NOS: 1, 13, 15 and 17. Appropriate correction is required.

Claim 17 is objected to because of the following informalities: it is composed of two sentences and thus does not comply with proper claim format as set forth in MPEP 608.01(m): "Each claim begins with a capital letter and ends with a period. Periods may

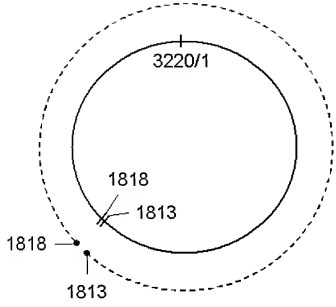
not be used elsewhere in the claims except for abbreviations." Appropriate correction is required.

Drawings

The drawings are objected to because figures 1, 2, 4 and 7 contain shading which obscures text (and plotted lines on the graph of figure 7) (see 37 CFR 1.84(m)). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Preliminary Note

The instant application and the prior art discussed in this Office action are directed to the synthesis of "greater-than-genome length" hepatitis B virus (HBV) constructs. The genome of HBV is a circular double-stranded DNA molecule. The instant application, as well as the prior art, will often refer to a fragment as comprising, e.g., "nucleotides 1818-1813" (see claim 3) or "nt 1686-660" (see Schories et al, Journal of Hepatology 33:799-811 (2000), page 802, column 1, "Fragment A"). Where the first number of the range is larger than the second number, this implies that the fragment extends from the first numbered position, through the HBV genome, across the junction of the last and first nucleotides of the genome, to the second numbered position. For example, assuming a genome size of 3220 nt, a fragment designated as 1818-1813 would correspond to the dotted segment below, shown in relation to the circular genome (where position 1818 represents the 5' end of the fragment, and position 1813 represents the 3' end of the fragment):



Note also that numbering of HBV nucleotide positions varies in the prior art; for example, the nucleotide designated as position 1 in one publication may not correspond to the nucleotide designated as position 1 in another publication.

Claim Interpretation

Limitations recited as "possibly" or "preferably" are considered optional and not distinguishing over the prior art. Claims 1, 5, 18 and 25 contain such language. For example, claim 1 will be interpreted as requiring only steps (b), (c), (d), (e) and (g) (and step (g) will be construed as only requiring "determining the replication capacity of the HBV"). Claims 29 and 30, which depend from claim 1 and further limit only the optional step (f), will be considered as requiring step (f). Where the prior art teaches any "optional" limitations, this will be pointed out in the rejection with the understanding that

such limitations are not required by the claims and therefore not required to be taught in the prior art.

The phrase "transcriptable in pgRNA" recited in claim 1, steps (b) and (c) will be construed as meaning that the "linear continuous DNA sequence" is able to be transcribed into pgRNA (pre-genomic RNA); see page 5, paragraph beginning "The present invention...such that a pgRNA can be synthesized from this DNA post-cell-transfection".

The term "incidence" in the phrase "possibly incidence of the pharmaceutical product, preferably antiviral agent, on viral gene expression and/or viral replication" recited in claim 1, step (g) will be assumed to mean "effect".

The term "the +1 of transcription" recited in claims 2, 5, 6 and 20 will be assumed to mean the nucleotide corresponding to the first nucleotide of the HBV pre-genomic RNA transcript.

The term "the ATG of the pre-C gene" recited in claim 2 will be assume to mean the ATG start codon of the pre-C gene (note that the pre-C gene comprises more than one ATG).

The terms "in 5' from" and "in 5' of" recited in claim 2 will be construed as "5' of".

The "about 1 genome unit" recited in claim 2 will be construed as a fragment of the circular HBV genome, wherein the 5' end of the fragment corresponds "the +1 of transcription" as discussed above, or to a nucleotide 5' thereof and 3' of the ATG start codon of the pre-C gene, wherein the fragment extends around the circular genome, across the junction of the first and last nucleotides of the genome, and terminates at a 3'

end corresponding to the nucleotide immediately preceding the "A" of the ATG start codon of the pre-C gene.

The "sub-genomic fragment" recited in claim 2 will be construed as a fragment of the circular HBV genome, wherein the 5' end of the fragment corresponds to the "A" of the ATG start codon of the pre-C gene, extends through "the +1 of transcription" as discussed above, and terminates at a 3' end corresponding to a nucleotide at or after the polyA attachment site.

The term "in 3' of" in claim 15 will be interpreted as "3' of".

Information Disclosure Statement

The references listed on the IDS submitted 06/16/2006 have been considered. The reference entitled "The Hepatitis B Virus Page" has been annotated on the PTO form 1449 to include the date shown on the printout supplied with the IDS.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Regarding claim 1, the term "e.g." in the preamble renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the

claimed invention. See MPEP § 2173.05(d). For purposes of examination over the prior art, the limitation "e.g. HBV present in a biological sample, possibly in the presence of a pharmaceutical product, preferably an antiviral agent" will not be considered required by the claim (see *Claim Interpretation*).

Also regarding claim 1, a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 recites the broad recitation "a pharmaceutical product" (in the preamble and steps (f) and (g)), and the claim also recites "an antiviral agent" (in the claim preamble and steps (f) and (g)), which is the narrower statement of the range/limitation.

Because claims 2-30 depend directly or indirectly from claim 1, they are rejected for the same reasons.

Regarding claim 17, this claim is composed of two sentences (which is improper form; see *Claim Objection* above). The second sentence reads: "From here numbers should be modified according to modification." It cannot be determined what this means. For purposes of examination over the prior art, the second sentence will be assumed to have been included erroneously.

Regarding claim 18, a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 18 recites the broad recitation 20-60, and the claim also recites 30-50, and preferably 40, which is the narrower statement of the range/limitation.

Regarding claim 25, the term "such as" in the phrase "such as hepatoma cells" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d). For purposes of examination over the prior art, the limitation "such as hepatoma cells" will not be considered required by the claim (see *Claim Interpretation*).

In addition, a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 25 recites the broad recitation "eucaryotic cells", and the claim also recites "preferably of hepatocyte origin, preferably cell lines such as hepatoma cells", which is the narrower statement of the range/limitation.

Because claims 26-28 depend from claim 25, they are rejected for the same reasons.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 20, 21 and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Junker et al (Nucleic Acids Research 15(24):10117-10132 (1987)) in view of the dissertation of Garces [online] publicly available on September 8, 2001 [retrieved on August 6, 2008], retrieved from:

http://proquest.umi.com/pqdweb?index=0&did=729292031&SrchMode=1&sid=1&Fmt=6&VInst=PROD&VType=PQD&RQT=309&VName=PQD&TS=1218309802&clientId=19649

and as evidenced by:

i) Weimer et al (Journal of Virology 61(10):3109-3113, October 1987)

ii) GenBank AB048704 [online] 23 March 2001 [retrieved on 6 August 2008] retrieved from http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nuccore&id=13365548

iii) Norder et al (Virology 198:489-503 (1994), cited on the IDS of 06/16/2006)

Evidence for the September 8th date for the Garces reference is provided in an email correspondence from Carol Wadke, supplied with this Office action.

With regard to claim 1, Junker taught a method of constructing a "greater-than-genome length" HBV construct (see figure 1) by cloning two fragments of HBV genomic DNA, which upon assembly represent a linear continuous DNA sequence "transcriptable in pgRNA", into a vector so producing a vector wherein transcription of pgRNA is under the control of a heterologous promoter (i.e. the human metallothionein II_A or "MT" promoter):

"First, the 2.3 kb BglII fragment 938-84 from pSHH2.1 was cloned into the BamHI site placing HBV position 938 near the HindIII site. Then, HBV sequences were completed by insertion of a HindIII-EcoRI fragment from plasmid pHTW3091 including HBV positions 3091-1280...The resulting plasmid was cut by SalI and HindIII and the MT promoter was inserted..." (paragraph bridging pages 10118-9, citations omitted).

"A slightly overlength HBV genome was cloned into the vector pUC13 between the unique HindIII and BamHI sites. This terminal redundant genome, starting 5' with the preC/C region and ending 3' with the HBV polyadenylation signal, contains all HBV genes in the order present in the pregenomic RNA. The human metallothionein II_A promoter was cloned in front of this genome. Thus, the constructs are expected to

synthesize RNA molecules equivalent to the HBV pregenome" (page 10121, first paragraph).

Aside from the fact that Junker did not obtain the fragments used to make this construct by PCR amplification, this meets the limitations of step (c) of claim 1.

Junker transfected susceptible cells with these vectors:

"Transfections were performed with 20 µg of DNA…" (page 10119, "Cells, immunoassays and protein analysis").

"In a first experiment, plasmid pMH3/3091 was introduced into HepG2 and HeLa cells…" (page 10121, "Transient expression in HeLa and HepG2 cells").

This meets the limitations of step (d) of claim 1.

In addition, Junker clearly stated: "Thus, the constructs are expected to synthesize RNA molecules equivalent to the HBV pregenome" (page 10121, first paragraph). An RNA molecule equivalent to the HBV pregenome can be considered a pre-genomic RNA (pgRNA).

This meets the limitations of step (e) of claim 1.

Finally, Junker taught determining the replication capacity of the HBV (e.g. measuring the amounts of various viral products produced; see figure 2 for example).

This meets the limitations of step (g) of claim 1, since, as stated in Applicant's specification (paragraph [0128] of the published application), determining the replication capacity of the HBV "may involve measuring the level of nucleic acid synthesis, protein synthesis, and/or virus production".

Note that steps (a), (f) and other limitations introduced by the term "possibly" are considered as optional and not distinguishing over the prior art (see *Claim Interpretation*).

With regard to claim 2, it is noted that the claimed "continuous DNA sequence" is indistinguishable from plasmid pMH3/3097 (see Junker figure 1). Junker describes in the first paragraph on page 10119: "Plasmid pMH3/3097 was derived from pMH3/3091 by replacing the HindIII-EcoRI HBV DNA fragment with the corresponding DNA fragment from pHTW3097 comprising HBV position 3097-1280 (9)." Reference 9 is the disclosure of Weimer et al.

Junker states on page 10121, second paragraph: "In addition, the preC start was eliminated in the third plasmid pMH3/3097 by deleting its first nucleotide...".

Thus, it is clear from the disclosure of Junker as evidenced by Weimer that position 3096 (using the numbering system of the Junker/Weimer references) corresponds to the "A" of the ATG start codon of the pre-C gene, while position 3097 corresponds to the "T". Therefore, the HBV sequence in Junker's pMH3/3097 began at the "T" of the ATG start codon of the pre-C gene and thus 5' of the "+1 of transcription" (the transcription start site for the pre-genomic RNA). In addition, as can clearly be seen from Junker's figure 1, the HBV sequence extends to and includes the polyA addition site. Hence, aside from the fact that Junker did not obtain the fragments used to make this construct by PCR amplification, this meets the limitations of claim 2.

With regard to claim 3, the limitations describing "the continuous DNA sequence" in terms of position numbers of "an HBV genomic sequence aligned with" GenBank AB048704 do not distinguish over the HBV sequence in Junker's pMH3/3097 for the following reasons:

i. The term "comprising" allows any additional sequence, either at the ends or interspersed within the continuous DNA sequence, so long as the continuous DNA sequence contains in a 5' to 3' order the sequences within the recited position numbers.

ii. The recited position numbers do not refer to GenBank AB048704 itself, but to any HBV sequence *aligned* with the GenBank sequence; hence it need not be shown that Junker's plasmid comprised the GenBank sequence within the recited position numbers, but only sequence *corresponding* thereto.

iii. The examiner aligned nucleotides 1813 to 1960 of Norder figure 1 with those of GenBank AB048704 and found the sequences to be corresponding:

```
CATGCAACTTTTTCACCTCTGCCTAATCATCTCTTGTACATGTCCCACTGTTCAAGCCTC
||||||||||||||||||||||||||||||||||| ||| |||||||| ||||||||||||||
CATGCAACTTTTTCACCTCTGCCTAATCATCTCATGTTCATGTCCTACTGTTCAAGCCTC

CAAGCTGTGCCTTGGGTGGCTTTGGGGCATGGACATTGACCCTTATAAAGAATTTGGAGC
||||  ||||||||||||||||||  || ||||||||||||||||||||||||||||||||||
CAAGTTGTGCCTTGGGTGGCTTTAGGACATGGACATTGACCCTTATAAAGAATTTGGAGC

TACTGTGGAGTTACTCTCGTTTTTGCCT
|  ||||||||||||||||  |||||||||
TTCTGTGGAGTTACTCTCTTTTTTGCCT
```

Hence, whatever aligns to the Norder sequence also aligns with the GenBank sequence in this region.

iv. The specification at page 7, last paragraph:

- an about 1-unit genome starting in 5' from and including the nucleotide representing the +1 of transcription (in general nucleotide A, position 1818 in H. Norder et al.; in some cases however, the +1 of transcription has revealed to be the nucleotide in 5' of said A, i.e. C, or in 3', i.e. A) to the first nucleotide in 5' of the ATG of the pre-C gene (nucleotide 1813 in H. Norder et al.), plus
- a sub-genomic fragment starting from and including the A of the ATG of the pre-C gene (nucleotide 1814 in H. Norder et al.) and extending to and including the polyA attachment site (nucleotide 1960 in H. Norder et al.), thus

Hence, Applicant identifies the "A" of the ATG start codon for the pre-C gene as position 1814 in the Norder sequence (which corresponds to position 1814 of the GenBank AB048704 sequence as well, i.e. the second nucleotide in the alignment shown above).

v. As discussed for claim 2 above, position 3097 (using Junker's numbering) corresponds to the "T" of the start codon of the pre-C gene, which in turn corresponds to position 1815 of the Norder figure 1 sequence, which in turn corresponds to position 1815 of the GenBank sequence.

Therefore, the continuous DNA sequence in Junker's pMH3/3097 begins with nucleotide 3097 (which corresponds to nucleotide 1815 of GenBank AB048704, according to the analysis discussed above), extends through the entire HBV genome, and ends the BglII site at nucleotide 84 (which corresponds to nucleotide 1984 of the GenBank AB048704, using the same analysis discussed above; see examiner's annotation on the GenBank printout). This being the case, Junker's continuous DNA

sequence *comprised* from 5' to 3', nucleotides 1818 to 1813 and 1814 to 1960 (with an additional 3 nucleotides at the 5' end and an additional 24 nucleotides at the 3' end) of an HBV genomic sequence aligned with the sequence as set forth in GenBank AB048704. Aside from the fact that Junker did not obtain the fragments used to construct pMH3/3097 by PCR amplification, this meets the limitations of claim 3.

With regard to claim 25, Junker taught hepatoma cells (see Abstract: "Transient expression of this construct in hepatoma cells..."; see also page 10121, section entitled "Transient expression in HeLa and HepG2 cells").

With regard to claim 26, Junker directly transfected the cells with the vector (page 10119, first paragraph under "Cells, immunoassays and protein analysis": "Transfections were performed with 20 μg of DNA...").

Junker did not teach PCR amplifying HBV nucleic acids using at least two primer pairs selected so as to obtain at least two different fragments as recited in claim 1.

Junker did not teach that the +1 of transcription of the heterologous promoter was fused to the +1 of transcription of the HBV fragment as recited in claim 20.

Junker did not teach any of the heterologous promoters recited in claim 21.

Junker did not teach transferring the vector into a baculovirus and then transducing the cells with the virus as recited in claim 27.

With regard to claims 1-3, Garces taught a method for constructing a greater-than-genome length HBV vector under control of a heterologous promoter (page 65). Specifically, a sub-genomic fragment beginning at the start codon of the core protein and extending to the unique HBV *Eco*RI site was amplified by PCR. This, along with a full-length genome fragment, were cloned under the control of the CMV promoter. See page 39 "wtHBV construct" for an illustration of the construct.

Garces did not explicitly teach that *both* fragments were obtained by PCR amplification; Garces is silent with respect as to how the full-length genomic fragment was obtained (see page 65: "...a linear full-length wild-type...genome was cloned to generate the greater-than-full length genome constructs".

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to synthesize the two fragments used by Junker to construct pMH3/3097 by PCR, thus arriving at the claimed invention, since the concept of using PCR to generate fragments to assemble into greater-than-genome length HBV sequences under control of a heterologous promoter was known as is clear from the disclosure of Garces. Although Garces only explicitly taught that one of the two fragments was made by PCR, one of ordinary skill in the art would have realized that if one fragment could be made by PCR, then the other fragment could also be synthesized in this way.

The use of PCR for obtaining fragments, as taught by Garces, may be regarded as an improvement over the earlier method of Junker, which relied on the pre-existence of suitable restriction sites as well as numerous steps including elimination of restriction

sites, addition of linkers, subcloning and site-directed mutagenesis to introduce restriction sites, all of which would have required several days if not weeks to accomplish (see paragraph bridging pages 10118-9 of Junker). Therefore, in light of Garces, it would have been obvious to use PCR to obtain fragments since this could have been accomplished more rapidly, avoiding dependence on pre-existing restriction sites or the need to generate them through mutagenesis.

In addition, PCR would have allowed any desired fragments to be amplified from the HBV genome, as well as allowing the addition of restriction sites to the ends of the amplified fragments simply by designing primers with the restriction sites already included (see for example section 2.2 of Garces, beginning on page 30, where Garces describes amplifying regions of the HBV genome with primers comprising NheI restriction sites, digesting the amplified products with NheI and cloning the products into vectors also digested with NheI). Thus it would have been obvious to apply the improvements and advantages of PCR as exemplified by Garces to the method for constructing the greater-than-genome length HBV construct taught by Junker.

With regard to claim 20, Junker discussed that the pre-genomic transcripts produced by the various constructs of his disclosure "differ with respect to sequence context and length at their 5'-ends and are different from the in vivo pregenomic RNA" (page 10130, second full paragraph; emphasis in original). Thus, it would have been *prima facie* obvious one of ordinary skill in the art at the time the invention was made to fuse the +1 transcription site of promoter to HBV sequence (as made possible by the advent of PCR) in order to re-create the naturally occurring in vivo pre-genomic RNA so

as to avoid any spurious effects cause by having additional sequence at the 5' end of the transcript.

With regard to claim 21, Garces teaches a greater-than-genome length construct under control of the cytomegalovirus immediate early (CMV-IE) promoter (page 38, section 2.10, first sentence). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention is made to substitute the CMV-IE promoter for the human metallothionein promoter in the construct of Junker, since both promoters were known in the art for controlling expression of HBV (see MPEP 2144.06).

With regard to claim 27, Garces transferred the construct into baculovirus which was then used to transduce (i.e. pseudo-infect) Hep G2 cells (page 66). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to insert the heterologous promoter-driven greater-than-genome-length HBV sequences taught by Junker into a baculovirus in order to transfer the vector into baculovirus and transduce the construct into cells. Garces taught that advantages of using baculovirus over transfection were simplicity and greater efficiency in terms of the ratio of cells expressing hepatitis B viral proteins (page 28).

Claims 4 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Junker et al (Nucleic Acids Research 15(24):10117-10132 (1987)) in view of the dissertation of Garces [online] publicly available on September 8, 2001 [retrieved on August 6, 2008], retrieved from:

http://proquest.umi.com/pqdweb?index=0&did=729292031&SrchMode=1&sid=1&Fmt=6&VInst=PROD&VType=PQD&RQT=309&VName=PQD&TS=1218309802&clientId=19649

and as evidenced by:

i) Weimer et al (Journal of Virology 61(10):3109-3113, October 1987)

ii) GenBank AB048704 [online] 23 March 2001 [retrieved on 6 August 2008] retrieved from http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nuccore&id=13365548

iii) Norder et al (Virology 198:489-503 (1994), cited on the IDS of 06/16/2006)

as applied to claims 1-3, 20, 21 and 25-27 above and further in view of Schories et al (Journal of Hepatology 33:799-811 (2000)). Note that the rejection of claims 4 and 17 rely on Norder not merely in an evidentiary manner, but also as a reference providing a teaching and motivation.

The teachings of Junker and Garces have been discussed. These references did not teach or suggest including the additional sequence downstream of the polyA site as indicated by the recited nucleotide position numbers in claim 4 (to arrive at the invention of claim 4, an additional 32 nucleotides would need to be added at the 3' end of the HBV sequence of Junker's pMH3/3097). Junker and Garces also did not teach or suggest using primers to regions "well conserved among HBV" as recited in claim 17.

Schories taught a method for constructing a full-length HBV genome from a patient by PCR amplifying overlapping fragments and assembling the fragments to obtain the sequence of the genome of this clinical HBV isolate (see Abstract and page 802, column 1). In particular, Schories stated (last sentence, page 801): "We therefore analyzed the sequence of multiple HBV clones from a patient with low-titered, immunologically negative HBV infection, and synthesized constructs with distinct mutations to investigate their influence on replication and expression of HBV antigens."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to practice the method suggested by the combined teachings of Junker and Garces (i.e. constructing pMH3/3097 as taught by Junker, but using PCR to obtain the fragments as taught by Garces) by obtaining the PCR amplified fragments from clinical samples in order to investigate the influence of mutations in such clinical isolates on replication, as taught by Schories, in order to better understand the biology of HBV and HBV infections. In order to do so, one would have been motivated to use primers to regions "well conserved among HBV" so as to be more likely to amplify fragments from any strain of HBV that might be present in the clinical sample. This meets the limitations of claim 17.

With regard to claim 4, it is noted that the region corresponding approximately to nucleotides 1966-1996 downstream of the polyA site does not appear to be well conserved (see figure 1 of Norder et al, which depicts considerable variability in this region among the six strains Norder investigated). However, the region corresponding to nucleotides 1997-2016 of the Norder sequence is more highly conserved (100% identical among five of the six strains Norder investigated). Therefore, in order to make use of primers to regions that were "well conserved among HBV", as discussed above, one of skill in the art would have been motivated to design a primer to this more highly conserved region downstream of the polyA site. Thus, the final product would have included the additional sequence corresponding to the nucleotide position numbers recited in claim 4.

Claims 5, 6 and 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Junker et al (Nucleic Acids Research 15(24):10117-10132 (1987)) in view of the dissertation of Garces [online] publicly available on September 8, 2001 [retrieved on August 6, 2008], retrieved from:

http://proquest.umi.com/pqdweb?index=0&did=729292031&SrchMode=1&sid=1&Fmt=6&VInst=PROD&VType=PQD&RQT=309&VName=PQD&TS=1218309802&clientId=19649

and as evidenced by:

i) Weimer et al (Journal of Virology 61(10):3109-3113, October 1987)

ii) GenBank AB048704 [online] 23 March 2001 [retrieved on 6 August 2008] retrieved from http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nuccore&id=13365548

iii) Norder et al (Virology 198:489-503 (1994), cited on the IDS of 06/16/2006)

as applied to claims 1-3, 20, 21 and 25-27 above and further in view of Hasegawa et al (Journal of Virology 68(3):1651-1659, March 1994).

The teachings of Junker and Garces have been discussed.

With regard to claim 5, since it would have been obvious to use PCR to generate the fragments when constructing the vector taught by Junker as already discussed, one would necessarily have had to use a pair of primers for each fragment amplified, wherein each pair comprised a forward and a reverse primer.

Furthermore, with regard to claims 5 and 6, since Junker specifically constructed a vector containing a greater-than-genome length HBV sequence with the +1 of transcription at the 5' end and the polyA site at the 3' end (see Junker figure 1, pMH3/3097) it would have been obvious that one fragment generated by PCR would have to comprise the +1 of transcription at the 5' end, while the other fragment would

have to comprise the polyA site at the 3' end, such that upon assembling these fragments, the structure shown in Junker figure 1 would have resulted. Therefore it would also have been obvious that the forward primer of one primer pair would contain the nucleotide representing the +1 of transcription (but not the ATG start codon of the pre-C gene), since this was what was what was found at the 5' end of the HBV sequence in Junker's pMH3/3097.

In addition, with regard to claim 6, the term "partially complementary" implies other than fully complementary. It would have been *prima facie* obvious to one of ordinary skill in the art to add restriction sites to the primers used for amplification of the fragments so as to allow for cloning into vectors. This well-known practice is demonstrated by Garces at section 2.2, beginning on page 30, where Garces describes amplifying regions of the HBV genome with primers comprising NheI restriction sites, digesting the amplified products with NheI and cloning the products into vectors also digested with NheI. By adding such restriction sites to the primers, one would have arrived at a primer that was "partially complementary", as recited in claim 6.

Neither Junker nor Garces taught generating "overlapping" fragments by PCR, wherein the overlapping region comprised a restriction site, as recited in claim 5, or the specific limitations concerning the primers and/or primer pairs recited in claims 10-15.

Hasegawa taught a method of constructing a full-length genome by PCR amplifying overlapping fragments (see section entitled "HBV constructs" beginning on page 1651). Hasegawa amplified three overlapping fragments corresponding to nucleotide positions 593-1676, 2263-843, and 1607-2430. Moreover, two of the

fragments were joined together by using a restriction site (SpeI) found within the region of overlap (position 681).

Therefore, with regard to claim 5, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to construct the HBV vectors taught by Junker by PCR amplifying overlapping fragments wherein a restriction site found within the region of overlap was used to join the fragments. This was a known technique for assembling HBV genomic fragments as demonstrated by Hasegawa.

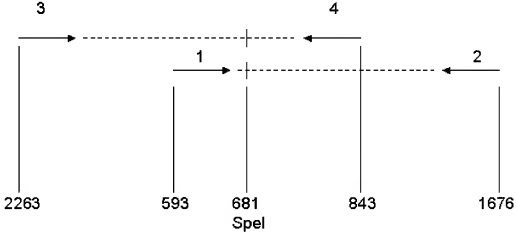
With regard to claim 10, it is noted that elected SEQ ID NO:13 was known as being found within the HBV genome as evidenced by GenBank AB048704:

```
Query  1372  CCATGGCTGCTAGGCTGTGCTGCC  1395
             ||||||||||||| |||||||||
Sbjct  24    CCATGGCTGCTAGGSTGTGCTGCC  1
```

(Note: "Query" is the GenBank sequence, whereas "Sbjct" is SEQ ID NO:13; "S" represents either C or G—see Specification page 12, next-to-last paragraph.) Thus, SEQ ID NO:13 would have been just as obvious a choice as any other known sequence in the HBV genome for amplifying a first fragment of HBV comprising the +1 transcription region.

With regard to claims 11 and 12, since it would have been obvious to amplify overlapping fragments for assembling the HBV sequence found in Junker's pMH3/3097 as already discussed, it would also have been obvious that the "forward" primer of the second pair would have been 5' of the "reverse" primer of the first pair, with respect to the positions of the primers within the genome. Otherwise, there would be a gap left in

the sequence. Hasegawa demonstrates this principle. Hasegawa's first primer set comprised a forward primer (primer 3) corresponding to nucleotide positions 2263-2287 and a reverse primer (primer 4) corresponding to nucleotide positions 823-843. Hasegawa's second primer set comprised a forward primer (primer 1) corresponding to nucleotide positions 593-617 and a reverse primer (primer 2) corresponding to nucleotide positions 1656-1676. These were used to amplify first and second fragments which were subsequently joined using the SpeI site found in the region of overlap (position 681; see Hasegawa page 1651, column 2, section entitled "HBV constructs" and examiner's illustration below):



As can be seen, the forward primer (1) of the second primer pair is 5' with respect to the reverse primer (4) of the first primer pair, and both primers are complementary to a region of HBV which comprises a natural restriction site (SpeI).

With regard to claim 13, it would have been obvious that any pair of overlapping fragments from the HBV genome could be amplified so long as they resulted, upon

assembly, in the greater-than-genome length HBV sequence of Junker's pMH3/3097. Thus, while the 5' end of the first fragment and the 3' end of the second fragment would be constrained with regard to the 5' and 3' ends, respectively, the choice as to where the two fragments would overlap would have been arbitrary, and all options would have been considered equivalent. Using the assembly technique of Hasegawa as a guide, one of skill would have seen that any region comprising a unique restriction site would have been a suitable region of overlap, and would have been able to design primers accordingly. Since, as evidenced by GenBank AB048704, the genome of HBV was known to contain a unique NcoI site (position 1372 of the GenBank sequence; see examiner's annotation on the GenBank printout), this, too, would have been an obvious place to design the overlap such that the fragments could be joined with that enzyme.

With regard to claim 14, it is noted that elected SEQ ID NO:15 was known as being found within the HBV genome as evidenced by GenBank AB048704:

```
Query  1363  ACCTCCTTTCCATGGCTGCTAGG  1385
             || || ||||||||||||||||||
Sbjct  1     ACMTCSTTTCCATGGCTGCTAGG  23
```

(Note: "Query" is the GenBank sequence, whereas "Sbjct" is SEQ ID NO:15; "S" represents either C or G—see Specification page 12, next-to-last paragraph; "M" represents either A or C—see Specification page 13, third paragraph.) Thus, SEQ ID NO:15 would have been just as obvious a choice as any other known sequence in the HBV genome for amplifying a second fragment. In fact, the elected primers SEQ ID NO:13 (claim 10) and 15 (claim 14) would have been more obvious than "any" sequences from the HBV genome since they comprise a unique NcoI site of the HBV

genome, and as discussed above, in light of Hasegawa's method of assembling fragments, making use of such a restriction site would have been standard technique.

With regard to claim 15, since Junker's pMH3/3097 comprised the polyA site at the 3' end (see Junker figure 1), it would have been obvious that a primer used to amplify a fragment comprising the polyA site would need to be located 3' of the polyA site in order to include the polyA site in the resulting PCR product.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Junker et al (Nucleic Acids Research 15(24):10117-10132 (1987)) in view of the dissertation of Garces [online] publicly available on September 8, 2001 [retrieved on August 6, 2008], retrieved from:

http://proquest.umi.com/pqdweb?index=0&did=729292031&SrchMode=1&sid=1&Fmt=6&VInst=PROD&VType=PQD&RQT=309&VName=PQD&TS=1218309802&clientId=19649

and Hasegawa et al (Journal of Virology 68(3):1651-1659, March 1994), and as evidenced by:

i) Weimer et al (Journal of Virology 61(10):3109-3113, October 1987)

ii) GenBank AB048704 [online] 23 March 2001 [retrieved on 6 August 2008] retrieved from http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nuccore&id=13365548

iii) Norder et al (Virology 198:489-503 (1994), cited on the IDS of 06/16/2006)

as applied to claims 5, 6 and 10-15 above and further in view of Jones (US 2002/0072055).

The teachings of Junker, Garces and Hasegawa have been discussed. In particular, Garces demonstrated that it was known in the art to design primers

comprising restriction enzyme sites to allow cloning of the resulting PCR products (see Garces at section 2.2, beginning on page 30, where Garces describes amplifying regions of the HBV genome with primers comprising NheI restriction sites, digesting the amplified products with NheI and cloning the products into vectors also digested with NheI).

Junker, Garces and Hasegawa did not explicitly teach a primer comprising a restriction site that is not present in the HBV genome as recited in claim 7.

Jones taught at paragraph [0044]: "Restriction endonuclease digestion is frequently used to generate cohesive ends for cloning DNA segments into a vector. This can be accomplished by attaching restriction endonuclease recognition domains to the ends of a DNA fragment by ligation of a linker or adaptor. Alternatively, a recognition domain can be incorporated into the end of a nucleic acid sequence using a primer whose 5' end contains the restriction endonuclease recognition site of interest, followed by primer directed synthesis of the opposite strand. One limitation inherent in such primer directed incorporation of a restriction endonuclease recognition domain is that the fragment of interest cannot contain the recognition domain for this enzyme if the intact fragment is to be cloned by digestion with this restriction endonuclease, as cutting of internal sites would generate shorter segments."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use restriction enzyme sites that were not found in the HBV genome when incorporating restriction enzyme sites into primers for amplifying

fragments used to assemble the vectors taught by Junker, since Jones demonstrates such a requirement would have been known by one of skill in the art.

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Junker et al (Nucleic Acids Research 15(24):10117-10132 (1987)) in view of the dissertation of Garces [online] publicly available on September 8, 2001 [retrieved on August 6, 2008], retrieved from:

http://proquest.umi.com/pqdweb?index=0&did=729292031&SrchMode=1&sid=1&Fmt=6&VInst=PROD&VType=PQD&RQT=309&VName=PQD&TS=1218309802&clientId=19649

Hasegawa et al (Journal of Virology 68(3):1651-1659, March 1994) and Jones (US 2002/0072055), and as evidenced by:

i) Weimer et al (Journal of Virology 61(10):3109-3113, October 1987)

ii) GenBank AB048704 [online] 23 March 2001 [retrieved on 6 August 2008] retrieved from http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nuccore&id=13365548

iii) Norder et al (Virology 198:489-503 (1994), cited on the IDS of 06/16/2006)

as applied to claim 7 above and further in view of Halle et al (USPN 6,303,308).

The teachings of Junker, Garces, Hasegawa and Jones have been discussed. These references did not teach or suggest the restriction enzymes recited in claim 8.

Halle demonstrates that all of these restriction enzymes were known in the prior art (column 3, lines 29-34).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use any of the enzymes recited in claim 8 for as unique restriction sites on the primers for amplifying HBV fragments, since all these enzymes

as well as the HBV genome sequence were known in the art. It would have been well within the skill of the ordinary artisan to determine which enzymes did not cut within the known HBV sequence, and the choice of any of the enzymes recited in claim 8 would have represented nothing more than the selection of a known material for its intended purpose (see MPEP 2144.07).

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Junker et al (Nucleic Acids Research 15(24):10117-10132 (1987)) in view of the dissertation of Garces [online] publicly available on September 8, 2001 [retrieved on August 6, 2008], retrieved from:

http://proquest.umi.com/pqdweb?index=0&did=729292031&SrchMode=1&sid=1&Fmt=6&VInst=PROD&VType=PQD&RQT=309&VName=PQD&TS=1218309802&clientId=19649

and as evidenced by:

i) Weimer et al (Journal of Virology 61(10):3109-3113, October 1987)

ii) GenBank AB048704 [online] 23 March 2001 [retrieved on 6 August 2008] retrieved from http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nuccore&id=13365548

iii) Norder et al (Virology 198:489-503 (1994), cited on the IDS of 06/16/2006)

as applied to claims 1-3, 20, 21 and 25-27 above and further in view of McLaughlin et al (US 2003/0104395).

The teachings of Junker and Garces have been discussed. These references did not teach or suggest any particular number of amplification cycles for amplifying fragments of HBV.

McLaughlin taught (paragraph [0060]): "PCR reaction time, temperatures and cycle numbers may be varied to optimize a particular reaction as a matter of routine experimentation."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the number of PCR cycles over the ranges recited in claim 18 as a matter of routine experimentation. As the court has stated, "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Junker et al (Nucleic Acids Research 15(24):10117-10132 (1987)) in view of the dissertation of Garces [online] publicly available on September 8, 2001 [retrieved on August 6, 2008], retrieved from:

http://proquest.umi.com/pqdweb?index=0&did=729292031&SrchMode=1&sid=1&Fmt=6&VInst=PROD&VType=PQD&RQT=309&VName=PQD&TS=1218309802&clientId=19649

and as evidenced by:

i) Weimer et al (Journal of Virology 61(10):3109-3113, October 1987)

ii) GenBank AB048704 [online] 23 March 2001 [retrieved on 6 August 2008] retrieved from http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nuccore&id=13365548

iii) Norder et al (Virology 198:489-503 (1994), cited on the IDS of 06/16/2006)

as applied to claims 1-3, 20, 21 and 25-27 above and further in view of Pachuk et al (Gene 243:19-25 (2000)).

The teachings of Junker and Garces have been discussed. These references do not teach or suggest cloning the fragments into a vector using a one-step cloning procedure.

Pachuk taught a one-step cloning procedure (see entire article).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a one-step cloning procedure to clone the amplified HBV fragments when constructing the vectors taught by Junker, because Pachuk taught his method "has made it possible to generate clones in one step that would require multiple steps by other methods" (page 25, last paragraph).

Claims 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Junker et al (Nucleic Acids Research 15(24):10117-10132 (1987)) in view of the dissertation of Garces [online] publicly available on September 8, 2001 [retrieved on August 6, 2008], retrieved from:

http://proquest.umi.com/pqdweb?index=0&did=729292031&SrchMode=1&sid=1&Fmt=6&VInst=PROD&VType=PQD&RQT=309&VName=PQD&TS=1218309802&clientId=19649

and as evidenced by:

i) Weimer et al (Journal of Virology 61(10):3109-3113, October 1987)

ii) GenBank AB048704 [online] 23 March 2001 [retrieved on 6 August 2008] retrieved from http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nuccore&id=13365548

iii) Norder et al (Virology 198:489-503 (1994), cited on the IDS of 06/16/2006)

as applied to claims 1-3, 20, 21 and 25-27 above and further in view of Wilson et al (USPN 6,001,557).

The teachings of Junker and Garces have been discussed. These references do not teach or suggest an actin promoter (as recited in claim 22), the chicken beta actin promoter (as recited in claim 23), or a beta actin associated with the CMV-IE enhancer (as recited in claim 24).

Wilson taught promoters for heterologous gene expression, including the CMV-IE promoter/enhancer and the CMV enhancer/chicken beta actin promoter (paragraph bridging columns 7-8). Furthermore, Wilson taught that the selection of such a promoter was a "routine matter" (column 7, line 65) and that "other promoter/enhancer sequences may be selected by one of skill in the art" (column 8, lines 10-12).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the metallothionein promoter used by Junker with the CMV enhancer/chicken beta actin promoter taught by Wilson, as doing so would have been a "routine matter" and would have represented nothing more than the substitution of one promoter known to be useful for expression of heterologous genes with another such promoter (see MPEP 2144.06).

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Junker et al (Nucleic Acids Research 15(24):10117-10132 (1987)) in view of the dissertation of Garces [online] publicly available on September 8, 2001 [retrieved on August 6, 2008], retrieved from:

http://proquest.umi.com/pqdweb?index=0&did=729292031&SrchMode=1&sid=1&Fmt=6&VInst=PROD&VType=PQD&RQT=309&VName=PQD&TS=1218309802&clientId=19649

and as evidenced by:

i) Weimer et al (Journal of Virology 61(10):3109-3113, October 1987)

ii) GenBank AB048704 [online] 23 March 2001 [retrieved on 6 August 2008] retrieved from http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nuccore&id=13365548

iii) Norder et al (Virology 198:489-503 (1994), cited on the IDS of 06/16/2006)

as applied to claims 1-3, 20, 21 and 25-27 above and further in view of Sells et al (Proc. Natl. Acad. Sci. USA 84:1005-1009, February 1987).

The teachings of Junker and Garces have been discussed. These references did not teach transferring the vector into a cell line in order to produce a stable cell line constitutively expressing HBV.

Sells taught transferring a plasmid bearing four tandem copies of the HBV genome into a cell line (HepG2) to produce a stable cell line constitutively expressing HBV (see Abstract: "HBV DNA is carried by these cells as chromosomally integrated sequences...", hence, stable).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to transfer the constructs made by Junker (using PCR to generate the fragments as suggested by Garces) into a cell line for the purpose of producing a "stable" cell line constitutively expressing HBV, since Sells taught that such a system can "be used to study the life cycle of HBV and the reaction of immunocompetent cells with cells carrying HBV" (see Abstract).

Claims 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Junker et al (Nucleic Acids Research 15(24):10117-10132 (1987)) in view of the

dissertation of Garces [online] publicly available on September 8, 2001 [retrieved on August 6, 2008], retrieved from:

http://proquest.umi.com/pqdweb?index=0&did=729292031&SrchMode=1&sid=1&Fmt=6&VInst=PROD&VType=PQD&RQT=309&VName=PQD&TS=1218309802&clientId=19649

and as evidenced by:

i) Weimer et al (Journal of Virology 61(10):3109-3113, October 1987)

ii) GenBank AB048704 [online] 23 March 2001 [retrieved on 6 August 2008] retrieved from http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nuccore&id=13365548

iii) Norder et al (Virology 198:489-503 (1994), cited on the IDS of 06/16/2006)

as applied to claims 1-3, 20, 21 and 25-27 above and further in view of Delaney et al (Antimicrobial Agents and Chemotherapy 43(8):2017-2026, August 1999).

The teachings of Junker and Garces have been discussed. These references did not teach the limitation of step (f), considered as optional in claim 1 but required in claims 29 and 30 (see *Claim Interpretation* above), or more particularly the antiviral agents recited in claim 29. The references did not teach testing a molecule as a potential antiviral agent as recited in claim 30.

Delaney taught a method wherein a recombinant baculovirus expressing HBV was transduced to HepG2 cells (see Abstract and page 2018, last paragraph prior to section entitled "Materials and Methods"). In addition, Delaney treated the cultured cells with lamivudine (3TC) following the transduction (see, e.g., Abstract: "We have investigated the antiviral properties of 3TC in vitro in HepG2 cells infected with recombinant HBV baculovirus"; see also page 2018, "Materials and Methods", "3TC treatment": "In experiments in which 3TC treatment was initiated after viral infection,

HepG2 cells were exposed to the indicated concentration of 3TC 24 h postinfection (p.i.) or 4 days p.i."). This meets the limitation of step f of claim 1 and the additional limitation of lamivudine in claim 29. Since Delaney stated the purpose was to investigate the antiviral properties in vitro, this also meets the limitations of claim 30, since even though lamivudine was known to be an antiviral agent, its antiviral properties in the particular system (baculovirus-transduced HepG2 cells) were unknown prior to Delaney's work; hence in that system, lamivudine represented a "potential antiviral agent". Moreover, Delaney concluded that "the HBV baculovirus-HepG2 system has specific advantages for drug studies and can serve as a complement to other in vitro model systems currently used for testing antiviral compounds" (last paragraph, page 2025).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to transfer the constructs made by Junker (using PCR to generate the HBV fragments as suggested by Garces) to a baculovirus vector and use these vectors to study known and potential antiviral agents as taught by Delaney. Both Garces and Delaney point out the advantages of a baculoviral-based approach for delivering HBV nucleic acid. Garces taught that advantages of using baculovirus over transfection were simplicity and greater efficiency in terms of the ratio of cells expressing hepatitis B viral proteins (page 28). Delaney taught that "advantages of the HBV baculovirus-HepG2 system include (i) the ability to initiate extremely high levels of HBV expression, (ii) a reproducible and precise control over the level of HBV expression, and (iii) the ability to rapidly detect HBV antigens, RNA, and both intracellular and extracellular DNA from low numbers of HepG2 cells" (page 2018, last

paragraph prior to "Materials and Methods"). One would have been motivated to apply the modified constructs of Junker to the purpose of testing antiviral compounds as proposed by Delaney in order to derive new therapies for treating HBV infections.

Conclusion

Claims 9 and 16 are free of the prior art as regards the elected SEQ ID NOS:1 and 17.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Examiner, Art Unit 1637